

## TABLE OF CONTENTS

Letter of Intent . . . . .	1-2
Table of Contents . . . . .	3
Scientific Rationale . . . . .	4-6
Preliminary Program . . . . .	7-8
Alphabetical List of Proposed Speakers and Chairs . . . . .	9-10
References . . . . .	11-12
Biographical Sketch - Michael H. Smolensky, Ph.D. . . . .	13-14
Biographical Sketch - Francesco Portaluppi, M.D. . . . .	15-16
Academy Background . . . . .	17-18
Board of Governors . . . . .	19-22
Project Budget . . . . .	23
Budget Justification . . . . .	24
501(c)(3) Form . . . . .	25
Current Annual Report . . . . .	26-38

## TIME-DEPENDENT STRUCTURE & CONTROL OF ARTERIAL BP

### INTRODUCTION:

Cardiovascular diseases constitute the leading causes of death in the United States, far beyond the number of deaths due to cancer. Approximately one-half the cardiovascular deaths is a consequence of high blood pressure (BP) (1). Thus, hypertension constitutes a significant medical and social problem. It is the subject of an extensive amount of basic research devoted to mechanisms as well as clinical trials of medications devoted to its control. Although meaningful advances have occurred in understanding the physiology of BP regulation by neural, cardiovascular, renal, and hormonal mechanisms, our work is far from complete. Research into the mechanisms of BP maintenance in health and disease states such as hypertension is also being strongly pursued. On the other hand, the facets and mechanisms of BP regulation *in relation to time*, especially in relationship to pathological and therapeutic implications, have received comparably little scientific attention until recently.

It has become increasingly evident, especially through the application of ambulatory BP monitoring technology (2), that BP varies in a time-dependent fashion; the temporal organization of BP variability encompasses a number of factors and mechanisms with specific time courses. Most scientists have focused on circadian (24-hour) and to some extent seasonal components of BP variability. Others have been concerned with ultradian components having periodicities of less than 24 hours (4-6). Recently, there has been an appreciation of the analogous temporal structure of cardiovascular functions as it relates to temporal patterns in pathological cardiovascular events (for review see ref. 7). In this regard, there has been a surge of scientific interest in the field of medical chronobiology as it pertains to cardiovascular disease, including hypertension. Moreover, there is growing appreciation for the role of circadian and other rhythms on the pharmacokinetics (chronokinetics) and pharmacodynamics (chronesthesia) of antihypertensive medications. Intriguingly enough, the time course of drug absorption and distribution need not coincide with the time course of drug effects on BP (7). This phenomenon, which is referred to chronesthesia, infers that drug effect is not simply a result of drug concentration per se: it can be dependent on a set of mechanisms which are also variable in time and which determine therapeutic results. A fascinating new field of research known as chronopharmacology (the study of biological rhythms and medications) has great clinical relevance, considering the aforementioned medical and social impacts of hypertension and cardiovascular accidents which all exhibit very specific time patterns.

The investigation of BP regulation and the underlying mechanisms must include the role of biological rhythms and other temporal factors which are influential. The results of such studies have clinical implications, especially in regard to the optimization of therapeutic interventions by timing antihypertensive medications to circadian or other biological rhythms (chronotherapeutics). Complete understanding of the chronobiologic and other mechanisms of BP rhythms in essential or secondary hypertension is still sought. Interest in the chronotherapy of hypertension is only in its infancy. The conference which is being held in Ferrara, Italy in September, 1995 is intended to stimulate multi-disciplinary scientific inquiry into the chronobiology and chronotherapy of hypertension. The proceedings of the New York Academy of Sciences conference, "Time-Dependent Structure and Control of Arterial Blood Pressure" is anticipated to have broad appeal since the subject matter explores topics of certain interest to both basic and applied scientists — physiologists, pharmacologists, clinicians, epidemiologists, biostatisticians, drug delivery and other pharmaceutical scientists plus regulatory personnel!

### CONFERENCE TOPICS AND ISSUES:

Five important topics and issues are to be addressed in depth at during the conference.

1) Analysis of the temporal structure of BP variability: this portion of the conference deals with the definitions and types of BP temporal patterns and the relative contribution of different rhythms to them. Animal (8.9) and human (10.11) models will be presented.

2) Mechanisms of temporal BP patterns and variability—what do we know and what should we investigate. This part reviews the contribution of neural, cardiovascular, renal, endocrine and behavioral rhythms. New data from ongoing studies will be presented to begin to address the contribution of circadian and other temporal patterns of blood flow to BP variability over the 24-hour and other time scales (12.13). Also, the contribution of "classical" (renin-angiotensin-aldosterone, cortisol) as well as novel hormonal and endothelial factors (atrial natriuretic peptide, calcitonin gene-related peptide, opioids, endothelins, nitric oxide) and their rhythms will be examined highlighting findings of the most recent studies (14-19). Finally, the role of exogenous behavioral factors on endogenous BP patterns will be addressed (19).

3) The pathophysiology of BP variability - what do we know and what should we investigate. This part will discuss the available epidemiological evidence which suggests that the rhythms of BP (as opposed to the levels) are prognostically important. This is probable, even though still unproven, given the relationships between the rhythms in BP and acute cardiovascular events (for review see ref. 20). Recent data will be presented on the pathological correlates (cardiac, cerebral, renal) of normal and altered BP rhythms (21-25). Two important matters will be addressed: (a) whether antihypertensive treatment should be programmed in time to achieve higher levels of medication in the morning for essential hypertension and in the evening for secondary hypertension and (b) whether a goal of treatment should be resetting the BP circadian rhythm in primary and secondary forms of hypertension.

4) Chronopharmacology and chronotherapeutics of BP - what do we know and what should we investigate. There is convincing evidence now, both from studies on animals and humans, that the pharmacokinetics of medications used for BP control exhibit administration-time-dependencies (26-28). Much less data are available (and they are all very recent) on the time-dependency of drug effects on essential and secondary forms of human hypertension (29-31). The few trials focusing on the time-dependent differences of antihypertensives have usually been limited in design to a comparison of morning vs. evening treatment. The rationale and methods of chronotherapeutic trials for hypertension will be discussed. The crucial issues to be addressed are: how does the current management of hypertension affect BP rhythms? How can the BP rhythms be modified in a time-specified manner? Is an individualized chronotherapy of hypertension possible? Is it desirable, and when? With regard to the latter issue, new data will be presented from ongoing studies of a new evening once-a-day calcium channel antagonist medication under trial in the United States (32).

5) The role of 24-hour arterial ambulatory BP monitoring in the evaluation of antihypertensive medications. This section of the conference addresses endpoint blood pressure parameters and statistical methods for BP data analysis and interpretation. The perspectives of the pharmaceutical industry and the regulatory agencies (for example, the Food and Drug Agency in the USA and comparable ones in Europe) regarding the chronobiology of hypertension and the chronopharmacology and chronotherapeutics of antihypertensives will be addressed in detail.

#### FORMAT OF THE CONFERENCE:

The conference will be divided into five separate sessions to cover the above topics. Neural mechanisms of BP rhythms will be discussed in Session I instead of Session II only for practical reasons, i.e. to leave adequate time for the evening poster session(s). A call for abstracts will be issued for this purpose, and submission from young investigators new to the field will be encouraged. Prominent scientists from the five continents (7 of 26 young and 3 women investigators) have agreed to contribute oral presentations and manuscripts to the proceedings. The proposed agenda of the September, 1995 meeting is appended. The proceedings and poster abstracts will be published in a future volume of the Annals of the New York Academy of Sciences distributed worldwide to over 700 institutional libraries and also offered to the Academy's 35,000

members. The volume is intended to serve both as a compendium of the present knowledge and stimulus for further research.

#### RELATED MEETINGS:

To our knowledge, during the last three years no other conference has covered this specific topic. The Fifth (1992) and the Sixth (1994) International Conference of Chronopharmacology and Chronotherapeutics which took place at the Amelia Island Plantation Conference Center, near Jacksonville, Florida, under the auspices of the International Society of Chronobiology, addressed the chronopharmacology and chronotherapy of antihypertensive medications to a limited degree. Only marginal consideration was given to the issues of BP rhythms and their control. The Society for Research on Biological Rhythms has also been gathering in Amelia Island for its biannual meeting, in 1992 and 1994, focusing mainly on non-clinical aspects of chronobiology. The meetings of the societies of hypertension and related fields, do include BP monitoring and/or BP control; however, the conference we propose is unique in its being focused not only on BP monitoring and BP variability, but on the specific matters and mechanisms relating to the chronobiology and chronotherapeutics of BP and hypertension. In conclusion, no other meeting or session held during the last three years (or scheduled for next year) has addressed the conference topic. Hence, researchers from various disciplines concerned with BP regulation and hypertension should find this conference unique and of great scientific interest.

# TIME-DEPENDENT STRUCTURE & CONTROL OF ARTERIAL BP

## Preliminary Program

### DAY 1

8:30 - 8:40 AM	Greetings
8:40 - 8:50 AM	Introductory Remarks (F Portaluppi-Ferrara, Italy)
8:50 - 12:30 AM <i>Session I:</i>	Blood pressure rhythms and their neural control <i>Session Chairs:</i> G Parati (Milano, Italy) and J Waterhouse (Manchester, England)
8:50 AM	High-frequency components of blood pressure variation (M Pagani-Milano, Italy)
9:20 AM	Ultradian rhythms of blood pressure associated with sleep and wakefulness (EB Raftery-Harrow, England)
9:50 AM	Circadian and infradian rhythms of blood pressure (G Cornelissen, Minneapolis, MN)
10:20 AM - 10:40 AM	Intermission
10:40	Neural mechanisms of blood pressure rhythms (G Parati-Milano, Italy)
11:10	Neurotransmitter systems and blood pressure rhythms (JP Chalmers-Bedford Park, Australia)
11:40	Signal transduction in animal models of normotension and hypertension (K Witte-Frankfurt, Germany)
12:10 - 12:30 PM	General Discussion
12:30 - 2:00 PM	Luncheon
2:00 - 4:20 PM <i>Session II:</i>	Vascular, renal, endocrine, and behavioural mechanisms of blood pressure rhythms <i>Session Chairs:</i> TG Pickering (New York, USA) and A Angelini (Torino, Italy)
2:00 PM	Vascular mechanisms of blood pressure rhythms (E Casiglia-Padova, Italy)

2:30 PM	Renal-hemodynamic mechanisms of blood pressure rhythms (J Cambar-Bordeaux, France)
3:00 PM	Endocrine mechanisms of blood pressure rhythms (F Portaluppi-Ferrara, Italy)
3:30 PM	Behavioral mechanisms of blood pressure rhythms (TG Pickering-New York, USA)
4:00 - 4:20 PM	General Discussion
4:30 - 6:30 PM	Poster Sessions

## DAY 2

### 8:30 AM - 12:30 PM Session III:

8:30 AM	Pathophysiology of blood pressure rhythms <u>Session Chairs:</u> Y Imai (Sendai, Japan) and F Portaluppi (Ferrara, Italy)
	Relationships of the circadian rhythms of thrombotic, ischemic, hemorrhagic and arrhythmic events to blood pressure rhythms (R Manfredini-Ferrara, Italy)
8:55 AM	Relationships of cardiac function and structure to blood pressure rhythms (D Rizzoni-Brescia, Italy)
9:20 AM	Relationships of cerebrovascular function and structure to blood pressure rhythms (Y Imai-Sendai, Japan)
9:45 AM	Relationships of renal function to blood pressure rhythms (J Staessen-Leuven, Belgium)
10:10 - 10:30 AM	Intermission
10:30 AM	Aging and blood pressure rhythms (E O'Brien-Dublin, Ireland)
10:55 AM	Pregnancy and blood pressure rhythms (F Carandente-Milano, Italy)
11:20 AM	Blood pressure rhythms in sleep disorders and dysautonomia (P Cortelli-Bologna, Italy)
11:45 AM	Blood pressure rhythms in transplanted patients (G Degaute-Bruxelles, Belgium)
12:10 - 12:30 PM	General Discussion
12:30 - 2:00 PM	Luncheon

### 2:00 - 4:00 PM Session IV:

2:00 PM	Chronopharmacology and chronotherapeutics of hypertension <u>Session Chairs:</u> Talma Rosenthal (Tel Aviv, Israel) and MH Smolensky (Houston, TX)
2:25 PM	Chronopharmacology of hypertension (B Lemmer-Frankfurt, Germany)
	Analysis of blood pressure rhythms for drug efficacy evaluation (G Germanò-Roma, Italy)
2:50 PM	Drug effects on BP rhythms in essential hypertension (T. Rosenthal-Tel Aviv, Israel)
3:15 PM	Drug effects on BP rhythms in secondary hypertension (M Middeke-Münich, Germany)
3:40 - 4:00 PM	General Discussion
4:00 - 4:20 PM	Intermission
4:20 - 6:20 PM Session V:	The role of arterial blood pressure monitoring (ABPM) in the evaluation of antihypertensive medications: procedural, statistical and regulatory issues <u>Session Chairs:</u> R Lapicky (FDA, Rockville, MD) and B Lemmer (Frankfurt, Germany)

4:20 PM	Chronobiologic perception of the role and need of ABPM (MH Smolensky-Houston, TX)
4:45 PM	Validation and statistical issues on the role and need of ABPM (Industry Speaker to be determined)
5:10 PM	Pharmaceutical industry perception of the role and need of ABPM (Industry Speaker to be determined)
5:35 PM	Regulatory perception of the role and need of ABPM (R Lapicky-Rockville, MD)
6:00 - 6:20 PM	General Discussion
6:20 PM - 6:30 PM	Closing Remarks (F Portaluppi-Ferrara, Italy)

### Alphabetical List of Proposed Speakers and Chairs

**NOTE:** *The following speakers are women: Franca Carandente, Germaine Cornelissen and Talma Rosenthal.*

The following speakers are young investigators (35 or younger): Edoardo Casiglia, Pietro Cortelli, Giuseppe Germanò, Roberto Manfredini, Massimo Pagani, Damiano Rizzoni, Klaus Witte.

- 1) Alberto Angeli, MD, PhD - Dept. of Internal Medicine, University of Torino Ospedale S. Luigi Gonzaga, I-10043 Orbassano (TO), Italy
- 2) Jean Cambar, PhD - Groupe d'Etude de Physiologie et de Physiopathologie Rénale Faculté de Pharmacie - 3 Place de la Victoire, F-33000 Bordeaux, France
- 3) Franca Carandente, MD, PhD - Chair of Chronobiology, University of Milano Istituto di Anatomia Umana Normale, via Mangiagalli 31, I-20100 Milano
- 4) Edoardo Casiglia, MD - Institute of Clinical Medicine, University of Padova v. Giustiniani 2, I-35128 Padova, Italy
- 5) John P. Chalmers, MD - Department of Medicine, Flinders Medical Center, Bedford Park, S. Australia 5042
- 6) Germaine Cornelissen, PhD - Chronobiology Laboratoires, 5-187 Lyon Laboratoires 420 Washington Avenue, S.E., Minneapolis, MN 55455, U.S.A.
- 7) Pietro Cortelli, MD - Institute of Neurology, University of Bologna via Ugo Foscolo 7 - I-40100 Bologna, Italy
- 8) Jean-Paul Degaute - Hypertension Clinic, University of Bruxelles Hôpital Erasme, 808 route de Lennik, 1070 Bruxelles, Belgium
- 9) Giuseppe Germanò - Internal Medicine, University "La Sapienza" I Clinica Medica, Policlinico Umberto I, viale del Policlinico, I-00161 Roma
- 10) Yutaka Imai, MD - Second Department of Medicine, Tohoku University School of Medicine Seiryō-Cho, Aoba-ku, Sendai 980, Japan
- 11) Dr. Raymond Lapicky Food and Drug Administration/Ceder/ODEI/HFD-110 5600 Fisher Lane, Rockville, MD 20852, U.S.A.
- 12) Björn Lemmer, MD, Ph - Zentrum der Pharmakologie, J.W. Goethe-Universität Theodor-Stern-Kai 7, D-60590 Frankfurt/M, Germany
- 13) Roberto Manfredini, MD - Institute of Internal Medicine, University of Ferrara S. Anna Hospital, Corso Giovecca 203, I-44100 Ferrara, Italy

14) Martin Middeke - Reha-Zentrum Spreewald  
Klinik für Herz- Kreislauf- und Stoffwechselerkrankungen - D-03096 Burg, Germany

15) Eoin T O'Brien, MD - Blood Pressure Unit, Department of Cardiology  
Beaumont Hospital - 9 Dublin, Ireland

16) Massimo Pagani, M.D. - Internal Medicine, University of Milano  
Ospedale L. Sacco, I-20157 Milano, Italy

17) Gianfranco Parati, MD - Scientific Institute S. Luca Hospital,  
Centro Auxologico Italiano  
via Spagnoletto 3, I-20149 Milano, Italy

18) Thomas G Pickering, MD, PhD - Cardiovascular Center, The New York Hospital  
Cornell Medical Center - 525 East 68th Street, New York, NY 10021, U.S.A.

19) Francesco Porta, MD - Hypertension Unit, Internal Medicine,  
University of Ferrara  
via Savonarola 9, I-44100 Ferrara, Italy

20) Edward B Raftery, MD - Department of Cardiology and  
Clinical Research Center  
Northwick Park Hospital, Harrow, Middlesex, United Kingdom

21) Damiano Rizzoni, MD - Internal Medicine, University of Brescia  
Ospedale Civile di Brescia, Piazza Spedali Civili 1, I-25100 Brescia, Italy

22) Talma Rosenthal, MD - Chorley Hypertension Unit, Chaim Sheba Medical Center,  
Tel Hashomer 52621, Israel.

23) Michael H Smolensky, PhD - School of Public Health, University of Texas  
Hermann Center for Chronobiology, 6410 Fannin, Suite 833, Houston, TX 77030, U.S.A.

24) Jan A Staessen, MD - Department of Pathophysiology, Catholic University of Leuven  
U.Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

25) Jim M Waterhouse, PhD - Dept. of Physiological Sciences, University of Manchester  
Stopford Building, Oxford Road, M13 9PT Manchester, United Kingdom

26) Klaus Witte, MD - Zentrum der Pharmakologie, J.W. Goethe-Universität  
Theodor-Stern-Kai 7, D-60590 Frankfurt/M, Germany

### References

1. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993; 153: 154-83.
2. Pickering TG. Ambulatory Monitoring and Blood Pressure Variability. Science Press, London, 1991.
3. Cornelissen G, Haus E, Halberg F. Chronobiologic blood pressure assessment from womb to tomb. In: Touitou Y, Haus E, eds. Biologic Rhythms in Clinical and Laboratory Medicine. Berlin: Springer-Verlag, 1992: 428-52.
4. Pagani M, Furlan R, Dell'Orto S, et al. Simultaneous analysis of beat by beat systemic arterial pressure and heart rate variabilities in ambulatory patients. J Hypertens 1985; 3(Suppl 3):S83-5.
5. Mancia G. Autonomic modulation of the cardiovascular system during sleep. N Engl J Med 1993; 328:347-9.
6. Staessen JA, Fagard R, Thijs L, et al. Fourier analysis of blood pressure profiles. Am J Hypertens 1993; 6:184S-187S.

7. Lemmer B. Cardiovascular chronobiology and chronopharmacology. In: Touitou Y, Haus E, eds. *Biologic Rhythms in Clinical and Laboratory Medicine*. Berlin: Springer-Verlag, 1992: 418-27.
8. Lemmer B, Mattes A, Böhm M, Ganzen D. Circadian blood pressure variation in transgenic hypertensive rats. *Hypertension* 1993; 22:97-101.
9. Sasaki S, Yoneda Y, Fujita H, et al. Association of blood pressure variability with induction of atherosclerosis in cholesterol-fed rats. *Am J. Hypertens* 1994; 7:453-9.
10. Degaute JP, an de Borne P, Linkowski P, et al. Quantitative analysis of the 24-hour blood pressure and heart rate patterns in young men. *Hypertension* 1991; 18:199-210.
11. Portaluppi F, Cortelli P, Avoni P, et al. Diurnal blood pressure variation and hormonal correlates in fatal familial insomnia. *Hypertension* 1994; 23:569-76.
12. de Leeuw PW, Gaillard CA. Circadian changes in the circulation. *High Blood Press* 1992; 1:245-7.
13. Casiglia E, Palatini P, Baccillieri MS, et al. Circadian rhythms of peripheral resistance. A non-invasive 24-hour study in young normal volunteers confined to bed. *High Blood Press* 1992; 1:249-55.
14. Portaluppi F, Trasforini G, Margutti A, et al. Circadian rhythm of calcitonin gene-related peptide in uncomplicated essential hypertension. *J Hypertens* 1992; 10:1227-34.
15. Portaluppi F, Vergnani L, degli Uberti EC. Atrial natriuretic peptide and circadian blood pressure regulation: clues from a chronobiological approach. *Chronobiol Int* 1993; 10: 176-89.
16. Portaluppi F, Vergnani L, Margutti A, et al. Modulatory effect of the renin-angiotensin system on the plasma levels of calcitonin gene-related peptide in normal man. *J Clin Endocrinol Metab* 1993; 77: 816-20.
17. Calhoun DA, Zhu S, Wyss JM, et al. Diurnal blood pressure variation and dietary salt in spontaneously hypertensive rats. *Hypertension* 1994; 24:1-7.
18. Bianchi S, Bigazzi R, Baldari G, et al. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. *Am J Hypertens* 1994; 7:23-9.
19. James GD, Pickering TG. The influence of behavioral factors on the daily variation of blood pressure. *Am J Hypertens* 1993; 6(6 Pt 2):S170-3.
20. Purcell HJ, Gibbs JS, Coats AJ, et al. Ambulatory blood pressure monitoring and circadian variation of cardiovascular disease; clinical and research applications. *Int J Cardiol* 1992; 36:135-49.
21. Verdecchia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, Porcellati C. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 1990; 81:528-536.
22. Rizzoni D, Muiyesan ML, Montani G, Zulli R, Calebieh S, Agabiti-Rosei E. Relationship between initial cardiovascular structural changes and daytime and nighttime blood pressure monitoring. *Am J Hypertens* 1992; 5:180-186.
23. Kuwajima I, Suzuki Y, Shimosawa T, Kanemaru A, Hoshino S, Kuramoto K. Diminished nocturnal decline in blood pressure in elderly hypertensive patients with left ventricular hypertrophy. *Am Heart J* 1992; 123:1307-1311.
24. Palanin P, Penso M, Racioppa A, Rugno E, Guzzardi G, Anacletio M, Pessina AC. Clinical relevance of nighttime blood pressure and of daytime blood pressure variability. *Arch Inter Med* 1992; 152:1855-1860.

25. Del Rosso G, Amoroso J, Santoferrara A, Fiederling B, Di Liberato L, Albertazzi A. Impaired blood pressure nocturnal decline and target organ damage in chronic renal failure. *J Hypertens* 1994; 12(Suppl 3):S15.

26. Lemmer B, Nold G, Behne S, et al. Chronopharmacokinetics and cardiovascular effects of nifedipine. *Chronobiol Int* 1991; 8:485-94.

27. Mattes A, Lemmer B. Effects of amlodipine on circadian rhythms in blood pressure, heart rate, and motility: a telemetric study in rats. *Chronobiol Int* 1991; 8:526-38.

28. Witte K, Weisser K, Neubeck M, et al. Cardiovascular effects, pharmacokinetics, and converting enzyme inhibition of enalapril after morning versus evening administration. *Clin Pharmacol Ther* 1993; 54:177-86.

29. Palatini P, Racioppa A, Raule G, et al. Effect of timing of administration on the plasma ACE inhibitory activity and the antihypertensive effect of quinapril. *Clin Pharmacol Ther* 1992; 52:378-83.

30. Palatini P, Mos L, Motolese M, et al. Effect of evening versus morning benazepril on 24-hour blood pressure: a comparative study with continuous intraarterial monitoring. *J Clin Pharmacol Ther* 1993, 31:295-300.

31. Potaluppi F, Vergnani L, Ambrosio MR, et al. Effect of isradipine sustained release on the circadian pattern of blood pressure in hypertension due to chronic renal failure. *Am J Hypertens* 1993; 6(5 part 2):99A, abs. 1262.

32. Weber MA, Anders RJ, MacIntyre JM, Smolensky MH. Antihypertensive efficacy of delayed release verapamil gastrointestinal therapeutic system (GITS) during the acceleration period (04:00-10:00) following nocturnal administration. Sixth International Conference of chronopharmacology and Chronotherapeutics, Amelia Island, Florida, July 5-9, 1994. Abstract Book, p. IIIb-10.

(12)

#### BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE		
Michael H. Smolensky	Professor of Environmental Sciences		
EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Illinois, Urbana, Illinois	B.S.	1964	Zoology
University of Illinois, Urbana, Illinois	M.S.	1966	Physiology
University of Illinois, Urbana, Illinois	Ph.D.	1971	Physiology

Smolensky, M.H. and G.E. D'Alonzo. Medical chronobiology: Concepts and Applications. Nocturnal Asthma, R. Martin (ed.), Futura Pub. Co., N.Y., pp. 1-23, 1993.

Smolensky, M.H. and G.E. D'Alonzo. Biological rhythms and medications: Chronopharmacology and chronotherapeutics. Nocturnal Asthma, R. Martin (ed.), Futura Pub. Co., N.Y., pp. 25-69, 1993.

D'Alonzo, G.E. and M.H. Smolensky. Chronobiology and chronotherapy of nocturnal asthma. Brit. J. Pharmacol. in press (1994).

D'Alonzo, G.E., M.H. Smolensky et al. Bambuterol in the treatment of asthma: a placebo-controlled comparison of morning versus evening administration. Chest in press (1994).

Smolensky, M.H. and M. Weber. Chronotherapy of mild hypertension by evening verapamil GITS. In preparation, JAMA (1994).

SELECTED EARLIER PUBLICATIONS:

Smolensky, M.H., I.A. Kraft, R.B. Sothern, T.D. Downs, C.W. Eisler and E.A. Mealy. Circadian rhythmicity in pulse rate and duration of cardiac cycle (P-P interval) in donor and recipient cardiac tissue of heart homograft patients. Texas Reports on Biology and Medicine 33(4):533-548, 1975.

Smolensky, M., S. Samueloff, B. Harley, E. McDonald and A. Reinberg. Circannual rhythm of cardiac mortality: An attempt to identify possible endogenous and exogenous factors. Israel J. Med. Sci. 12(8):818-827, 1976.

Cech, I., M.H. Smolensky, R. Lane, B. Harley and S. Samueloff. Biometeorologic aspects of short-term fluctuations of cardiac mortality in Jerusalem and Tel-Aviv studied by lagged cross-covariance analysis. Israel J. Med. Sci. 12(8):828-831, 1976.

Smolensky, M.H., S.A. Bergman, C.N. Barnard, W. Beck and I. Kraft. Circadian rhythmic characteristics of innervated and non-innervated cardiac tissues of single and double-heart transplanted patients. Cardiovascular Disease Bulletin, Texas Heart Institute 3(2):150-168, 1976.

Cech, I., and M.H. Smolensky. Daily and seasonal cardiovascular mortality patterns in Houston. Cardiovascular Disease Bulletin, Texas Heart Institute 3(4):370-381, 1976.

Hartung, H.O., M.H. Smolensky, R. Harrist and C. Skrovan. Effects of varied durations of physical training on improvement in cardiorespiratory endurance. J. Human Ergol. 6:61-68, 1977.

Smolensky, M.H., S.E. Tatar, S.A. Bergman, J.G. Losman, C.N. Barnard, C.C. Dacso and I.A. Kraft. Circadian rhythmic aspects of cardiovascular function. A review by chronobiologic statistical methods. Chronobiologia 3:337-371, 1977.

Smolensky, M., J. Jovanovich, G. Kyle and B. Hsi. Chronotoxicity in rodents challenged with propranolol HCL (Inderal). In: Chronopharmacology, A. Reinberg and F. Halberg (eds.). Pergamon Press, Oxford, 1979, pp. 263-271.

Smolensky, M.H., A. Reinberg and J. Queng. Chronobiology and chronopharmacology of allergy. Ann. Allergy 47(4):234-252, 1981.

Reinberg, A., M.H. Smolensky and F. Levi. Therapeutic implications of time dependencies. In: Topics in Pharmaceutical Sciences 1985, Elsevier Science Publishers B.V. (Biomedical Division), 1985, pp. 191-205.

Reinberg A., M.H. Smolensky and G. Labrecque. New aspects in chronopharmacology. Ann. Rev. Chronopharmacol. 2:3-26, 1986.

Smolensky, M.H., P.H. Scott and W. Kramer. Clinical significance of day-night differences in serum theophylline concentration with special reference to TheoDur. J. Allergy Clin. Immunol. 78: 716-722, 1986.

Smolensky, M.H., P.J. Barnes, A. Reinberg and J.P. McGovern. Chronobiology and asthma. I. Day-night differences in bronchial patency and dyspnea and circadian rhythm dependencies. J. Asthma 23(6):321-343, 1986.

Randem, B., M.H. Smolensky, B. Hsi, D. Albright and S. Burge. Field survey of circadian rhythm in PEF of electronics workers suffering from colophony-induced asthma. Chronobiology Internat'l. 4(3):263-272, 1987.

Smolensky, M.H., J.P. McGovern, P.H. Scott and A. Reinberg. Chronobiology and asthma. II. Day-night differences in the kinetics and effects of bronchodilator medications. J. Asthma 24(2):91-134, 1987.

Smolensky, M.H. Chronobiology and epidemiology. Pathol. Biol. 35(6):991-1004, 1987.

Reinberg, A., M.H. Smolensky, G. Labrecque and M. Hallek. Aspects of chronopharmacology and chronotherapy in children. Chronobiologia 14:303-325, 1987.

Reinberg, A., M.H. Smolensky, G.E. D'Alonzo and J.P. McGovern. Chronobiology and asthma. III. Timing corticotherapy to biological rhythms to optimize treatment goals. J. Asthma 25(4):219-248, 1988.

Smolensky, M.H. Medical chronobiology. Amer. J. Medicine 85(Suppl 1b): 34-46, 1988.

Albright, D., A. Voda, M.H. Smolensky, B.P. Hsi and M. Decker. Circadian rhythm in hot flash in natural and surgically induced menopause. Chronobiol. Internat'l. 6:279-284, 1989.

## BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE		
FRANCESCO PORTALUPPI	Assistant Professor of Internal Medicine Head of Hypertension Unit		

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Ferrara, Ferrara, Italy	M.D.	1977	Medicine
Oak Forest Hospital, Chicago Medical School/ Univ. of Health Sciences, Chicago, Illinois, USA	Research Fellow	1979/80	Cardiology
University of Ferrara, Ferrara, Italy	Diploma of Specialization	1981	Cardiology
University of Milano, Milano, Italy	Postdoctoral Diploma	1986	Chronobiology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, or honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Cardiology Resident, University of Ferrara (Italy): 1981- 1989

Internal Medicine Resident, University of Ferrara (Italy): November 1990-Present

Head of Hypertension Unit, Internal Medicine, University of Ferrara, Ferrara (Italy): 1992- Present

Member of the Board of the European Society for Chronobiology; Member of the Nominating Committee of the International Society for Chronobiology; Member of the Editorial Board of Chronobiology International; reviewer for Kidney International

### PAPERS DURING THE PAST THREE YEARS

1. Portaluppi F, Montanari L, Massari M, Di Chiara V, Capanna M. Loss of nocturnal decline of blood pressure in hypertension due to chronic renal failure. Am J Hypertens 1991;4(1 Pt 1):20-26.
2. Portaluppi F, Bagni B, Cavallini AR, Calisesi M, Valpondi V, Montanari L, Mollica G. Plasma levels of atrial natriuretic peptide are increased in normotensive postmenopausal women as a function of age. Cardiology 1991;78(4):317-322.
3. Portaluppi F, Montanari L, Vergnani L, degli Uberti E. Effects of the converting enzyme inhibitor quinapril on autonomic function in normotensive and essential hypertensive subjects. Curr Ther Res 1991;50(2):231-238.
4. Portaluppi F, Montanari L, Ferlini M, Vergnani L, D'Ambrosi A, Cavallini AR, Bagni B, degli Uberti E. Consistent changes in the circadian rhythms of blood pressure and atrial natriuretic peptide in congestive heart failure. Chronobiol Int 1991;8(5):432-439.
5. Trasforini G, Margutti A, Portaluppi F, Menegatti M, Ambrosio MR, Bagni B, Pansini R, Degli Uberti EC. Circadian profile of plasma calcitonin gene-related peptide in healthy man. J Clin Endocrinol Metab 1991;73(5):945-951.
6. Portaluppi F, Montanari L, Vergnani L, Taroni G, Cavallini AR, Gilli P, Bagni B, degli Uberti EC. Loss of nocturnal increase in plasma concentration of atrial natriuretic peptide in hypertensive chronic renal failure. Cardiology 1992;80(5-6):312-323.
7. Portaluppi F, Montanari L, Ferlini M, Vergnani L, Bagni B, Degli Uberti EC. Differences in blood pressure regulation of congestive heart failure, before and after treatment, correlate with changes in the circulating pattern of atrial natriuretic peptide. Eur Heart J 1992;13(7):990-996.
8. Degli Uberti EC, Salvadori S, Trasforini G, Margutti A, Ambrosio MR, Rossi R, Portaluppi F, Pansini R. Effect of deltorphin on pituitary-adrenal response to insulin-induced hypoglycemia and ovine corticotropin-releasing hormone in healthy man. J Clin Endocrinol Metab 1992;75(2):370-374.
9. Portaluppi F, Trasforini G, Margutti A, Vergnani L, Ambrosio MR, Rossi R, Bagni B, Pansini R, degli Uberti EC. Circadian rhythm of calcitonin gene-related peptide in uncomplicated essential hypertension. J Hypertens 1992;10(10):1227-1234.
10. Portaluppi F, Cortelli P, Avoni P, Sforza E, Vergnani L, degli Uberti EC, Lugaresi E. Circadian rhythms of blood pressure and heart rate in fatal familial insomnia. J Interdiscipl Cycle Res 1992;23(3):227-229.
11. degli Uberti EC, Salvadori S, Trasforini G, Margutti A, Ambrosio MR, Rossi R, Portaluppi F, Vergnani L, Pansini R.  $\delta$ -Opioid receptors and the secretion of growth hormone (GH) in man: Effect of opioid  $\delta$ -receptor

agonist deltorphin on GH responses to GH-releasing hormone and insulin-induced hypoglycemia. *Neuroendocrinology* 1992;56(6):907-912.

12. Fontani G, Vergnani L, Salvadori S, Voglino N, Aloisi AM, Portaluppi F, degli Uberti EC. Effect of dermorphin on behavior and hippocampal electrical activity in rabbits. *Life Sci* 1993;52(3):323-8.
13. Fontani G, Vergnani L, Salvadori S, Voglino N, Aloisi AM, Portaluppi F, Degli Uberti EC. Effect of deltorphin on behavior and hippocampal electrical activity in rabbits. *Physiol Behav* 1993 Feb;53(2):285-90.
14. Portaluppi F, Vergnani L, degli Uberti EC. Atrial natriuretic peptide and blood pressure regulation. Clues from a chronobiological approach. *Chronobiol Int* 1993;10(3):176-189.
15. Portaluppi F, Vergnani L, Margutti A, Ambrosio MR, Bondanelli M, Trasforini G, Rossi R, Degli Uberti EC. Modulatory effect of the renin-angiotensin system on the plasma levels of calcitonin gene-related peptide in normal man. *J Clin Endocrinol Metab* 1993;77(3):816-20.
16. degli Uberti EC, Ambrosio MR, Vergnani L, Portaluppi F, Bondanelli M, Trasforini G, Margutti A, Salvadori S. Stress-induced activation of sympathetic nervous system is attenuated by the selective  $\delta$ -opioid receptor agonist deltorphin in healthy man. *J Clin Endocrinol Metab* 1993;77(6):1490-1494.
17. Portaluppi F, Cortelli P, Avoni P, Sforza E, Vergnani L, degli Uberti EC, Lugaresi E. Loss of sleep activity and circadian rhythms of blood pressure in fatal familial insomnia. *J Hypertens* 1993;11 (Suppl 5):S469-S470.
18. Trasforini G, Margutti A, Vergnani L, Ambrosio MR, Valentini A, Rossi R, Portaluppi F, degli Uberti EC. Evidence that enhancement of cholinergic tone increases basal plasma levels of calcitonin gene-related peptide in normal man. *J Clin Endocrinol Metab* 1994;78(3):763-766.
19. Portaluppi F, Cortelli P, Avoni P, Vergnani L, Contin M, Maltoni P, Pavani A, Sforza E, degli Uberti EC, Gambetti P, Lugaresi E. Diurnal blood pressure variation and hormonal correlates in fatal familial insomnia. *Hypertension* 1994;23(5):569-576.
20. Portaluppi F, Cortelli P, Avoni P, Vergnani L, Maltoni P, Pavani A, Sforza E, degli Uberti EC, Gambetti P, Lugaresi E. Progressive disruption of the circadian rhythm of melatonin in fatal familial insomnia. *J Clin Endocrinol Metab* 1994;78(5):1075-1078.
21. Manfredini R, Gallerani M, Portaluppi F, Salmi R, Chierici F, Fersini C. Circadian variation in the occurrence of paroxysmal supraventricular tachycardia in clinically healthy subjects. *Chronobiol Int* 1994;11:in press.
22. Portaluppi F, Manfredini R, degli Uberti EC, Fersini C. Time-dependent effect of isradipine on the nocturnal hypertension of chronic renal failure. *Am J Hypertens* 1994;7:in press.

#### REPRESENTATIVE EARLIER PAPERS

1. Portaluppi F, degli Uberti E, Strozzì C, Margutti A, Montanari L, Rambaldi R, Trasforini G, Pansini R. Slow-release nifedipine: effect on the circadian rhythm of blood pressure in essential hypertension. *Acta Cardiol* 1987;42(1):37-47.
2. Portaluppi F, Strozzì C, degli Uberti E, Rambaldi R, Trasforini G, Margutti A, Montanari L, Fersini C, Pansini R. Does placebo lower blood pressure in hypertensive patients? A noninvasive chronobiological study. *Jpn Heart J* 1988;29(2):189-197.
3. Portaluppi F, Montanari L. Consistency of circadian blood pressure pattern assessed by non-invasive monitoring and cosinor analysis in hospitalized hypertensive patients. *Acta Cardiol* 1988;43(5):605-613.
4. Portaluppi F, Montanari L, Capanna M, Ferlini M. Chronobiologic vs. sphygmomanometric assessment of hypertension in a hospital setting. *Clin Cardiol* 1989;12(7):380-383.
5. Portaluppi F, Montanari L, Bagni B, degli Uberti E, Trasforini G, Margutti A. Circadian rhythms of atrial natriuretic peptide, blood pressure and heart rate in normal subjects. *Cardiology* 1989;76(6):428-432.
6. Portaluppi F, Montanari L, Ferlini M, Capanna M. Are we overtreating hypertensive patients? Chronobiologic vs. sphygmomanometric evaluation of ambulatory antihypertensive therapy. *Jpn Heart J* 1990;31(1):35-41.
7. Portaluppi F, Bagni B, degli Uberti E, Montanari L, Cavallini R, Trasforini G, Margutti A, Ferlini M, Zanella M, Parti M. Circadian rhythms of atrial natriuretic peptide, renin, aldosterone, cortisol, blood pressure and heart rate in normal and hypertensive subjects. *J Hypertens* 1990;8(1):85-95.
8. Portaluppi F, Pradella A, Montanari L, Degli Uberti E, Trasforini G, Margutti A, Cavallini AR, Bagni B. Atrial strain is the main determinant of release of atrial natriuretic peptide. *Int J Cardiol* 1990;29(3):297-303
9. Portaluppi F, Montanari L, Pansini R. Effects of the converting enzyme inhibitor quinapril on the circadian rhythm of blood pressure and heart rate in essential hypertension. *Curr Ther Res* 1990;48(4):613-622.
10. Portaluppi F, Montanari L, Ferlini M, Gilli P. Altered circadian rhythms of blood pressure and heart rate in non-hemodialysis chronic renal failure. *Chronobiol Int* 1990;7(4):321-327.

# The New York Academy of Sciences

## Founding, Membership, and Independence

The Academy, founded in 1817, is now in its 179th year. It is the third oldest scientific society in America and one of New York City's oldest and most enduring cultural institutions. The Academy's mission includes complimentary commitments to science and society through leadership in both ideas and in programs of action. In service to science, it will sharpen its efforts to facilitate exchanges among scientists in New York and around the world. In service to society, it is expanding its activities in public communication, policy-debate, and science education to illuminate and improve the quality, timeliness, and reliability of contributions of science to global social and economic progress. Today, it is an international organization with over 43,500 members in more than 150 countries--nearly fifty percent of whom reside outside the United States. With a balanced annual operating budget of just under \$10 million, and little governmental support, the Academy has an unusual degree of independence.

## Plans for the 1990s

In December 1993, the Academy's Board of Governors adopted a strategic plan that builds on and expands the Academy's position at the intersection of science, business, education, health care, and government. In December 1994, the Plans were reviewed and updated with clear priorities and action plans.

## Conferences and Publications

Approximately 20-30 scientific conferences are held annually in locations around the world. A new emphasis on presenting the metropolitan region as a global science and technology center is resulting in more conferences being scheduled in New York. Conference proceedings are published in the Academy's *Annals*, which are among the oldest (172 years) and most frequently quoted sources of scientific research. About 30 *Annals* are distributed each year to more than 745 libraries and to thousands of scientists and engineers worldwide. Additionally, the Academy publishes *The Sciences*, a bi-monthly magazine with a circulation of almost 75,000. *The Sciences* has earned many national awards for scientific and artistic distinction in presenting scientific information to an educated lay public. With a lead grant from the Esther A. and Joseph Klingenstein Fund, the Academy will issue a series of publications on science policy issues drawn from meetings of its Science Policy Association.

## Science Policy and Economic Development

Since 1985, the Academy has sponsored a Science Policy Association that brings together leaders of business, education, philanthropy, the professions, policy-makers, government officials, scientists, and engineers to discuss policy-related issues at the intersection of science, technology, education, and economic development.

Science and technology serving economic development--in the New York region as well as in national and global policy--is a rising priority of the Academy. Through policy analysis and through outreach, prestige, and the ability to convene experts from a variety of disciplines, the Academy aims to share experiences, problems, and solutions.

## K-12 Science and Math Education

The Academy's programs support science teachers and teaching in the City's--and the region's--public, private, and parochial schools. They encourage about 3,000 students and teachers to do science, provide internships in corporate, government, and other laboratories, encourage achievement through the Academy's six annual Science and Technology Expos for students in grades 5-12, and seek to advance public awareness of science, technology, and issues such as infrastructure and competitiveness. The Academy recently published the first directory of professional science and educational development opportunities for science teachers and is looking to design and implement a new series of initiatives for teachers. Our education priorities are motivation and presentation of opportunities and initiatives leading to a more scientifically literate and prepared workforce. We bring the talents of scientists, social scientists, and engineers to the K-12 education process as mentors for students and teachers, and as catalysts for improvement and change in science education in the City's public schools. A Junior Academy for high school students was established in 1963 and now has about 1,000 members.

### Science and Engineering Across Disciplines

Differing from traditional professional organizations, the Academy seeks to function at the intersection of disciplines and issues. Through sections in twenty-four scientific and engineering areas, the Academy provides continuing education opportunities whereby scientists meet with the leaders in their and other fields. More than 180 meetings of scientists and engineers are held annually at the Academy's headquarters. Sections on Science Education, and on Women in Science, cross all disciplinary boundaries to focus on opportunities and special needs in these crucial areas. Section meetings are open to the public without charge.

### The Lyceum Club

In 1993, the Academy sponsored the founding of the Lyceum Club, a program for retired and semi-retired Academy members that provides daytime discussion programming and a talent bank of highly skilled individuals whose services are available to school, non-profit, for-profit, and government agencies.

### Human Rights of Scientists

The Academy has an active program which promotes the human rights of scientists, physicians, engineers, and educators irrespective of the political or economic policies of the countries in which such individuals reside. The Academy was credited by Andrei Sakharov and Fang Lizhi with coordinating the international pressure that led to their release. Both made their first U.S. appearances at the Academy. Today, with the Committee of Concerned Scientists, the Academy is assisting emigree scientists from the former Soviet Union, the Peoples' Republic of China and other countries to adjust to and find positions in the U.S. while simultaneously working on behalf of scientists worldwide to ensure the free pursuit of scientific careers and free expression. And we continue to work on behalf of scientists such as Vil Mirzayanov of Russia, whose work to eliminate chemical weapons testing has proved the rule of the new Russian constitution.

### The Gallery of Art and Science

In fall, 1994, the Academy formalized its longstanding exhibition program of art and science with the appointment of a curator and establishment of an alliance with the State University of New York at Binghamton. The opening exhibition, *Madness in America*, received an enthusiastic and extensive review in *The New York Times*. Programs change throughout the year; the public is invited without charge.

### The New York Academy of Sciences – organization, support, and leadership

The New York Academy of Sciences is located at Two East Sixty-third Street, New York, New York. Open to all who are interested in science, it is a non-profit 501(c)(3) supported by membership dues, publication and magazine sales, and from the gifts of corporations, foundations, members, and friends around the world. It sponsors a thriving Corporate Membership program, and collaborates with corporation, foundations, individuals, and other organizations in presenting science-based programs for the public good.

The Academy has a Board of Governors of distinguished individuals from all sectors. The Board, and the Academy's president, chief executive officer, and staff benefit strongly from the President's Council which is comprised of individuals of extraordinary accomplishment and with broad expertise who are chosen for their leadership in fields important to the Academy's mission. Academy committees draw heavily on leaders from business, education, and the non-profit sector, advancing the Academy's work as the center where people, ideas, and issues in science and technology-based social and economic development converge.



# THE NEW YORK ACADEMY OF SCIENCES

## Chairman of the Board

*Dr. Joshua Lederberg*

Raymond & Beverly Sackler Foundation  
Scholar and University Professor  
The Rockefeller University  
1230 York Avenue  
New York, NY 10021

## President

*Dr. Henry M. Greenberg*

Associate Professor of Clinical Medicine  
Columbia University  
College of Physicians & Surgeons  
and  
Director, Coronary Care Unit  
St. Luke's Roosevelt Hospital Center  
425 West 59th Street  
New York, New York 10019

## President-Elect

*Dr. Martin L. Leibowitz*

Managing Director  
Salomon Brothers, Inc.  
7 World Trade Center  
41st Floor  
New York, New York 10048

## Treasurer

*Mr. Henry A. Lichstein*

Vice President  
Citibank, N.A.  
399 Park Avenue  
New York, NY 10043

## Governors

*Dr. Eleanor Baum*

Dean, School of Engineering  
The Cooper Union  
51 Astor Place  
New York, New York 10003

*Dr. Barry R. Bloom*

Professor, Weinstock Professor  
Department of Microbiology and Immunology  
Albert Einstein College of Medicine  
1300 Morris park Avenue  
Bronx, NY 10461

*Dr. D. Allan Bromley*

Professor of Physics  
Yale University  
New Haven, CT 06520

*Mr. Edward Cohen*

Chairman, CEO, Managing Partner  
Ammann & Whitney, Inc.  
96 Morton Street  
New York, New York 10014-3309

*Dr. Susanna Cunningham-Rundles*

Associate Professor of Immunology  
Cornell University Medical College  
1300 York Avenue  
New York, New York 10021

*Mr. Bill Green*

Director  
N.Y.C. Housing Development Corporation  
75 Maiden Lane  
New York, NY 10038

**Governors (cont.)**

*Dr. Sandra Panem*

Managing Partner  
Vector Fund Management L.P.  
17-51 lake Cook Road  
Suite 350  
Deerfield, IL 60015

*Dr. Richard A. Raskind*

Chairman, Sloan-Kettering Institute  
Memorial Sloan-Kettering Cancer Center  
1275 York Avenue  
New York, New York 10021

*Dr. Dominick Salvatore*

Professor and Director of  
Graduate Program  
Department of Economics  
Fordham University  
Bronx, New York 10461

*Dr. David E. Shaw*

Managing General Partner  
D.E. Shaw & Co.  
120 West 45th Street  
39th Floor  
New York, New York 10036

*Mr. William C. Steere, Jr.*

President & CEO  
Pfizer, Inc.  
235 East 42nd Street  
New York, New York 10017-5755

*Dr. Shmuel Winograd*

Director, mathematical Sciences Dept.  
TJ Watson Research Center  
P.O. Box 218  
Yorktown Heights, New York 10598

**Past Chairman**

*Dr. Cyril M. Harris*

Charles Bachelor Professor Emeritus  
of Electrical Engineering  
Columbia University  
New York, New York 10027

**Honorary Life Governor**

*Mr. William T. Golden*

40 Wall Street  
Room 421  
New York, New York 10005

**General Counsel**

Ex-Officio

*Mrs. Helen L. Kaplan*

Skadden, Arps, Slate, Meagher & Flom  
919 Third Avenue  
New York, New York 10022

**Chief Executive Officer**

Ex-Officio

*Mr. Rodney W. Nichols*

The New York Academy of Sciences  
2 East 63rd Street  
New York, New York 10021

**Secretary**

Ex-Officio

*Ms. Svetlana Kostic-Stone*

The New York Academy of Sciences  
2 East 63rd Street  
New York, New York 10021

## Project Budget

### Salaries

Conference Director	\$ 1,800.00
Development Manger	\$ 1,260.00
Conference Coordinator	\$ 5,880.00
Administrative Assistant	\$ 2,275.00
Promotion Coordinator	\$ 1,767.00
	\$ 12,982.00
Benefits (31%)	\$ 4,024.00

### Conference Expense

Conference Promotion	\$ 6,000.00
Typesetting and Printing	\$ 2,200.00
Postage and Shipping	\$ 2,500.00
Conference Materials	\$ 1,000.00
Conference Facility Rental	\$ 3,000.00
AV Technician/Audio Taping	\$ 3,000.00
Receptionist	\$ 1,000.00
Speakers' Food Function	\$ 1,000.00
Reproduction Expenses	\$ 400.00
	\$ 20,100.00

### Travel

Staff Travel	\$ 3,000.00
Domestic Speakers' Travel	\$ 4,500.00
Foreign Speaker's Travel	\$ 10,000.00
Speakers' Per Diem (\$150.00/night - 3)	\$ 8,100.00
Supplemental Support:	
Junior Faculty 2X500	\$ 1,000.00
Graduate Students 2X500	\$ 1,000.00
Minority Attenders 2X500	\$ 1,000.00
	\$ 28,600.00

### Publications

Annals	\$ 18,000.00
SUB-TOTAL	<u>\$ 83,706.00</u>

### Academy Expense (12%)

Rent	
Utilities	
Telephone	
Fax	
General Administration	\$ 10,045.00
TOTAL	<u>\$ 93,751.00</u>

### Conference Sources of Support

SmithKline Beecham	\$ 1,500.00
Bristol Mayer Squibb (23)	\$ 2,000.00

## Budget Justification

1)	Speakers' Travel and Per Diem	\$ 1,700.00
2)	Junior Investigators, graduate students and Minority Attenders	\$ 1,800.00
3)	Conference Promotion: Paid Advertisements in special journals, purchase of mailing list, promotional brochures	<u>\$ 1,500.00</u>

Total requested funds: \$ 5,000.00

**Internal Revenue Service**

District  
Director

**Department of the Treasury**

10 MetroTech Center  
625 Fulton Street  
Brooklyn, NY 11201

▷

New York Academy  
of Sciences  
2 East 63rd Street  
New York, NY  
10021-7289

Date: OCT 15 1992

Person to Contact:  
Patricia Holub  
Contact Telephone Number:  
(718) 488-2333  
EIN: 13-1773640

Dear Sir or Madam:

Reference is made to your request for verification of the tax exempt status of New York Academy of Sciences.

A determination or ruling letter issued to an organization granting exemption under the Internal Revenue Code remains in effect until the tax exempt status has been terminated, revoked or modified.

Our records indicate that exemption was granted as shown below.

Sincerely yours,



Patricia Holub  
Manager, Customer  
Service Unit

Name of Organization: New York Academy of Sciences

Date of Exemption Letter: March 1936

Exemption granted pursuant to section 501(c)(3) of the Internal Revenue Code.

Foundation Classification (if applicable): Not a private foundation as you are an organization described in section 509(a)(2) of the Internal Revenue Code.

## **Combined Financial Statements**

The New York Academy of Sciences  
and The American Institute of Science  
and Technology of the  
City of New York

*Years ended June 30, 1994 and 1993  
with Report of Independent Auditors*

ERNST & YOUNG LLP

The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York

Combined Financial Statements

Years ended June 30, 1994 and 1993

Contents

Report of Independent Auditors .....	1
Combined Balance Sheets .....	2
Combined Statements of Support, Revenue, Expenses and Changes in Fund Balances .....	3
Combined Statements of Cash Flows .....	4
Notes to Combined Financial Statements .....	5

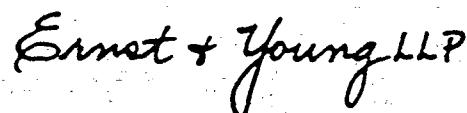
**Report of Independent Auditors**

Boards of Governors  
The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York

We have audited the accompanying combined balance sheets of The New York Academy of Sciences and The American Institute of Science and Technology of the City of New York (collectively, the "Academy") as of June 30, 1994 and 1993, and the related combined statements of support, revenue, expenses and changes in fund balances and cash flows for the years then ended. These financial statements are the responsibility of the Academy's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with generally accepted auditing standards. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the combined financial position of The New York Academy of Sciences and The American Institute of Science and Technology of the City of New York at June 30, 1994 and 1993, and the combined results of their operations and their cash flows for the years then ended in conformity with generally accepted accounting principles.



August 29, 1994

The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York

Combined Balance Sheets

	June 30	
	1994	1993
<b>Assets</b>		
Cash and cash equivalents	\$ 749,000	\$1,159,000
Receivables:		
Sales of publications, less allowance for doubtful accounts of \$33,000 in 1994 and \$39,000 in 1993	631,000	645,000
Grants	240,000	209,000
Other	284,000	140,000
Investments ( <i>Note 2</i> )	<b>1,954,000</b>	1,104,000
Prepaid expenses and deferred costs	146,000	132,000
Property and equipment, at cost, net of accumulated depreciation and amortization ( <i>Note 3</i> )	830,000	813,000
Total assets	<b>\$4,834,000</b>	<b>\$4,202,000</b>
<b>Liabilities and fund balances</b>		
Accounts payable and accrued liabilities	\$1,088,000	\$ 821,000
Deferred membership dues and conference registration fees	1,630,000	1,547,000
Deferred subscription revenue	799,000	692,000
Deferred support ( <i>Note 4</i> )	716,000	649,000
Total liabilities	<b>4,233,000</b>	3,709,000
Commitments ( <i>Note 7</i> )		
Fund balances (deficit) ( <i>Note 5</i> ):		
Unrestricted:		
The New York Academy of Sciences	(84,000)	(188,000)
The American Institute of Science and Technology of the City of New York	29,000	25,000
Total unrestricted	<b>(55,000)</b>	(163,000)
Restricted	-	-
Endowment	656,000	656,000
Total fund balances	<b>601,000</b>	493,000
Total liabilities and fund balances	<b>\$4,834,000</b>	<b>\$4,202,000</b>

*See accompanying notes.*

**The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York**

**Combined Statements of Support, Revenue, Expenses  
and Changes in Fund Balances**

	<b>Year ended June 30</b>	
	<b>1994</b>	<b>1993</b>
<b>Support and revenue</b>		
Membership dues	\$2,930,000	\$2,933,000
Publication sales and advertising	3,385,000	3,060,000
Grants and contributions for conferences and publications, and conference registration fees	1,186,000	1,372,000
Educational program contributions	386,000	344,000
Special program fees and contributions	290,000	267,000
Other grants and contributions	736,000	589,000
Investment income	34,000	68,000
Total support and revenue	<b>8,947,000</b>	<b>8,633,000</b>
<b>Expenses</b>		
Program services:		
Membership maintenance	643,000	457,000
Publications	4,217,000	3,923,000
Conferences	1,374,000	1,554,000
Educational programs	577,000	442,000
Special programs	599,000	825,000
Total program services	<b>7,410,000</b>	<b>7,201,000</b>
Supporting services:		
Membership recruitment	720,000	678,000
Fund raising	420,000	340,000
General and administrative expenses, including interest expense of \$18,000 in 1993	289,000	301,000
Total supporting services	<b>1,429,000</b>	<b>1,319,000</b>
Total expenses	<b>8,839,000</b>	<b>8,520,000</b>
Excess of support and revenue over expenses	108,000	113,000
Total fund balances—beginning of year	493,000	380,000
Total fund balances—end of year	<b>\$ 601,000</b>	<b>\$ 493,000</b>

*See accompanying notes.*

**The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York**

**Combined Statements of Cash Flows**

	<b>Year ended June 30</b>	
	<b>1994</b>	<b>1993</b>
<b>Cash flows from operating activities</b>		
Excess of support and revenue over expenses	\$ 108,000	\$ 113,000
Adjustments to reconcile excess of support and revenue over expenses to net cash provided by operating activities:		
Depreciation and amortization	145,000	209,000
Amortization of bond discounts	(8,000)	(21,000)
Unrealized depreciation (appreciation) on investments	7,000	(18,000)
Changes in operating assets and liabilities:		
Increase in receivables	(161,000)	(162,000)
(Increase) decrease in prepaid expenses and deferred costs	(14,000)	35,000
Increase (decrease) in accounts payable and accrued liabilities	267,000	(186,000)
Increase in deferred membership dues and conference registration fees	83,000	21,000
Increase in deferred support	67,000	196,000
Increase in deferred subscription revenue	107,000	168,000
Net cash provided by operating activities	<b>601,000</b>	<b>355,000</b>
<b>Cash flows from investing activities</b>		
Purchases of investments	(3,568,000)	(1,708,000)
Sales of investments	2,719,000	1,547,000
Purchase of fixed assets	(162,000)	(92,000)
Net cash used by investing activities	<b>(1,011,000)</b>	<b>(253,000)</b>
<b>Cash flows from financing activities</b>		
Repayment of debt	-	(373,000)
Net cash used by financing activities	<b>-</b>	<b>(373,000)</b>
Net decrease in cash and cash equivalents	(410,000)	(271,000)
Cash and cash equivalents—beginning of year	1,159,000	1,430,000
Cash and cash equivalents—end of year	<b>\$ 749,000</b>	<b>\$ 1,159,000</b>

*See accompanying notes.*

The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York

Notes to Combined Financial Statements

June 30, 1994

**1. Organization, Basis of Presentation and Significant Accounting Policies**

**Organization and Basis of Presentation**

The accompanying combined financial statements include the accounts of The New York Academy of Sciences and The American Institute of Science and Technology of the City of New York (the "Institute") (collectively, the "Academy"), two not-for-profit scientific and educational organizations that are under common control. Both organizations are Section 501(c)(3) organizations, exempt from Federal income taxes under Section 501(a) of the Internal Revenue Code.

**Fund Accounting**

To ensure observance of limitations and restrictions placed on the use of resources available to the Academy, the accounts of the Academy are maintained in accordance with the principles of fund accounting. This is the procedure by which resources for various purposes are classified for accounting and reporting purposes into funds established according to their nature and purposes. In the accompanying financial statements, the Academy has combined the activities of the following fund groups:

- Operating funds, which include unrestricted and restricted resources, represent the portion of expendable funds that is available for support of the Academy's operations.
- Endowment funds represent funds that are subject to restrictions of gift instruments, requiring in perpetuity that the principal be invested and only the income be used.

**Restricted Resources**

Various organizations and other parties award grants and make contributions to the Academy to assist in defraying expenses in connection with conferences, special projects, educational programs and other endeavors. Resources restricted by the donor, grantor or other outside contributor for particular operating purposes are deemed to be earned and reported as revenue when the Academy has incurred expenditures in compliance with the specific restrictions, subject to the Academy's revenue and expense recognition policies related to future conferences and special projects (see below). Amounts received but not yet earned are reported as deferred support.

The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York

Notes to Combined Financial Statements (continued)

**1. Organization, Basis of Presentation and Significant Accounting Policies (continued)**

**Membership Dues and Subscription Revenue**

Membership privileges include, among other things, a subscription to the Academy's magazine, *The Sciences*, and the ability to participate in the Academy's conferences and meetings and receive certain other publications. The Academy does not allocate its membership dues among the various membership privileges.

Membership dues and subscription revenue are recognized as revenue over the respective membership and subscription periods. Deferred membership dues and deferred subscription revenue relate to amounts received that apply to future periods.

In fiscal 1993, the Academy changed its accounting policy to recognize subscription revenue from nonmember subscriptions of *The Sciences* over the subscription period. In prior years, such revenue was recognized on a cash basis. The effect of this change is not material to the accompanying financial statements.

**Conferences and Special Projects**

Revenue and expenses related to conferences and special projects are recognized upon completion of the conference or special project.

**Property and Equipment**

Property and equipment are recorded at cost. Depreciation and amortization are provided on a straight-line basis over the estimated useful lives of the related assets or, for leasehold improvements, the shorter of the estimated useful lives or the terms of the related leases.

**Cash Equivalents**

The Academy considers all highly liquid investments purchased with a maturity of three months or less to be cash equivalents. Mutual funds held in the Academy's investment portfolio are not considered to be cash equivalents.

The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York

Notes to Combined Financial Statements (continued)

**1. Organization, Basis of Presentation and Significant Accounting Policies (continued)**

**Investments**

Investments in U.S. Treasury bills and notes are recorded at amortized cost. Investments in mutual funds are recorded at market value.

**Functional Allocation of Expenses**

The costs of providing the various programs and other activities have been summarized on a functional basis in the statements of support, revenue, expenses and changes in fund balances. Accordingly, certain costs have been allocated among the programs and supporting services benefited. In fiscal 1994, the Academy revised its allocation of general and administrative expenses among program and supporting services categories to more accurately reflect such relationships. The accompanying fiscal 1993 functional expenses have been reclassified to conform to the fiscal 1994 presentation.

**2. Investments**

Investments consist of the following at June 30, 1994 and 1993:

	1994	1993	
	Carrying Cost	Carrying Value	Carrying Cost
U.S. Treasury bills and notes (carrying value approximates market value)	\$ 904,000	\$ 904,000	\$ 679,000
Brandywine Funds	197,000	186,000	-
Scudder Growth and Income Fund	384,000	387,000	-
Vanguard Fixed Income Securities Fund	477,000	477,000	404,000
Total investments	<u>\$1,962,000</u>	<u>\$1,954,000</u>	<u>\$1,083,000</u>
			<u>\$1,104,000</u>

**The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York**

**Notes to Combined Financial Statements (continued)**

**3. Property and Equipment, at Cost**

Property and equipment, at cost, consist of the following at June 30, 1994 and 1993:

	<b>1994</b>	<b>1993</b>
Land	\$ 266,000	\$ 266,000
Building and improvements	648,000	648,000
Furniture, fixtures and equipment	782,000	717,000
Computer equipment and software	585,000	488,000
Leasehold improvements	175,000	175,000
	<b>2,456,000</b>	<b>2,294,000</b>
Less accumulated depreciation and amortization	1,626,000	1,481,000
Net property and equipment	<b>\$ 830,000</b>	<b>\$ 813,000</b>

**4. Deferred Support**

Following is the activity in deferred support for the years ended June 30, 1994 and 1993:

	Scholarship Funds	Prize Funds	Grants and Other Revenue Applicable to Future Projects	Total Deferred Support
Balance at July 1, 1992	\$ 54,000	\$ 82,000	\$ 317,000	\$ 453,000
Additions:				
Restricted contributions	51,000	37,000	1,382,000	1,470,000
Deductions:				
Revenue recognized for restricted funds expended	-	20,000	1,254,000	1,274,000
Balance at June 30, 1993	105,000	99,000	445,000	649,000
Additions:				
Restricted contributions	-	1,000	1,212,000	1,213,000
Deductions:				
Revenue recognized for restricted funds expended	-	-	1,146,000	1,146,000
Balance at June 30, 1994	<b>\$ 105,000</b>	<b>\$100,000</b>	<b>\$ 511,000</b>	<b>\$ 716,000</b>

The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York

Notes to Combined Financial Statements (continued)

**5. Fund Balances**

The following is a summary of the changes in fund balances (deficit) for the years ended June 30, 1994 and 1993:

	Unrestricted Funds	Restricted Funds	Endowment Funds	Total Funds
Fund balances, July 1, 1992, as previously reported	\$ 130,000	\$ -	\$ 150,000	\$ 280,000
Restatement (see below)	(406,000)	-	506,000	100,000
Fund balances (deficit), July 1, 1992, as restated	(276,000)	-	656,000	380,000
Excess of support and revenue over expenses	113,000	-	-	113,000
Fund balances, June 30, 1993	(163,000)	\$ -	656,000	493,000
Excess of support and revenue over expenses	108,000	-	-	108,000
Fund balances (deficit), June 30, 1994	\$ (55,000)	\$ -	\$ 656,000	\$ 601,000

During fiscal 1993, the Academy determined that certain borrowings made in prior years from the endowment funds principal balances to the unrestricted funds had been erroneously recorded as fund balance transfers. The Academy has restated the unrestricted and endowment fund balances (deficit) as of June 30, 1992 to properly reflect the prior years' transactions as interfund borrowings. In addition, the Academy has restated the endowment fund balance as of June 30, 1992 to properly include an endowment pledge made in a prior year. As of June 30, 1994 and 1993, interfund borrowings aggregated approximately \$406,000. The Academy intends to explore various alternatives to repay the interfund borrowings or, if possible, to eliminate the restrictions of the related gift instruments.

**6. Line of Credit**

As of June 30, 1993, the Academy had available a \$500,000 line of credit with a bank. There were no borrowings under the line at June 30, 1993. During fiscal year 1994, the line of credit arrangement was terminated.

The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York

Notes to Combined Financial Statements (continued)

**7. Commitments**

**Lease Commitment**

The Academy leases office space under the terms of an operating lease agreement that expires in September 1995. Future minimum rental commitments under the terms of the lease are approximately \$37,000 in fiscal 1995 and \$7,000 in fiscal 1996.

Rent expense aggregated approximately \$47,000 and \$39,000 for the years ended June 30, 1994 and 1993, respectively.

**Pension Plan**

Retirement benefits for eligible employees are provided through individual annuities with Teachers Insurance and Annuity Association. Pension expense was approximately \$272,000 and \$260,000 for the years ended June 30, 1994 and 1993, respectively, and represents the cost of individual insured annuities for each of the covered employees.

**8. The American Institute of Science and Technology of the City of New York**

The Institute administers grants awarded by the New York State Department of Agriculture and distributes these grants as awards to various individuals. The balance sheet and statement of revenue and expenses of the Institute as of and for the year ended June 30, 1994 and 1993 are as follows:

**Balance Sheet**

	<b>June 30</b>	
	<b>1994</b>	<b>1993</b>
<b>Assets</b>		
Cash	\$ 15,000	\$ 15,000
Grant receivable	14,000	10,000
<b>Total assets</b>	<b>\$ 29,000</b>	<b>\$ 25,000</b>
 <b>Fund balance</b>	 <b>\$ 29,000</b>	 <b>\$ 25,000</b>

The New York Academy of Sciences and  
The American Institute of Science and  
Technology of the City of New York

Notes to Combined Financial Statements (continued)

**8. The American Institute of Science and Technology of the City of New York  
(continued)**

Statement of Revenue and Expenses

Contributions	\$ 19,000	\$ 13,000
Awards	15,000	13,000
Excess of revenue over expenses	<u>\$ 4,000</u>	<u>\$ -</u>

**9. Accounting for Contributions and Financial Statement Display**

In June 1994, the Financial Accounting Standards Board issued Statement of Financial Accounting Standards No. 116, *Accounting for Contributions Received and Contributions Made* ("SFAS 116"), and Statement of Financial Accounting Standards No. 117, *Financial Statements of Not-for-Profit Organizations* ("SFAS 117").

SFAS 116 establishes standards of accounting for contributions and applies to all entities that receive or make contributions. Among other things, SFAS 116 requires contributions received and unconditional promises to give to be recognized as revenue in the period received at their fair values. Conditional promises to give are to be recognized when they become unconditional; that is, when the conditions are substantially met.

SFAS 117 establishes broad standards for reporting information in general-purpose external financial statements issued by not-for-profit organizations, and requires that all not-for-profit organizations provide a statement of financial position, a statement of activities, and a statement of cash flows that focus on the entity as a whole. Amounts related to an organization's financial position and activities are to be reported in three classes of net assets—permanently restricted, temporarily restricted, and unrestricted.

SFAS 116 and 117 will be effective no later than for the Academy's fiscal year ending June 30, 1996. Management believes that SFAS 116 and 117 will not have an adverse impact on its financial position, although SFAS 117 will require a change in the presentation of its financial statements.